

Comparison of Dexmedetomidine/Morphine and Xylazine/Morphine as Premedication in Isoflurane-Anesthetized Sheep

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In this study we investigated the sedative, anesthetic, and pulmonary histopathologic effects of dexmedetomidine/morphine (DM) and xylazine/morphine (XM) in sheep. We hypothesized that DM would provide profound sedation and better maintain physiologic parameters under anesthesia than XM in sheep undergoing laparoscopic surgery. Nineteen male sheep were premedicated with either DM (dexmedetomidine [0.006 mg/kg] and morphine [0.3 mg/kg]) or XM (xylazine [0.1 mg/kg] and morphine [0.3 mg/kg]). After DM or XM administration, 3 blinded veterinarians evaluated sedation scores (0 [no sedation], 1 [mild], 2 [moderate], 3 [severe]). Sheep were induced with intravenous tiletamine/zolazepam, intubated, and maintained with isoflurane in 100% oxygen. Anesthetic parameters were monitored for 60 min, including heart rate, respiratory rate, indirect blood pressure, oxygen saturation, end-tidal carbon dioxide, body temperature, arterial blood gas analysis, and isoflurane requirement. At the end of the procedure, the sheep were euthanized, and lung pathology (pulmonary edema) was assessed. The results showed that the sedation scores did not differ between DM (0.8 [0.4 to 1.0]) and XM (1.0 [1.0 to 1.0]). In addition, the anesthetic parameters were comparable between the groups, but the DM group exhibited a higher heart rate than the XM group. Finally, marked pulmonary changes, consistent with pulmonary edema, were observed in the XM group. In conclusion, DM and XM provided similar sedation and physiologic stability under isoflurane anesthesia, but DM may help minimize bradycardia and was associated with less evidence of pulmonary edema.

Abbreviations and Acronyms: DAP, diastolic arterial pressure; DM, combination of dexmedetomidine and morphine; EtCO₂, end-tidal carbon dioxide; HR, heart rate; MAP, mean arterial pressure; PaO₂, partial pressure of arterial O₂; RR, respiratory rate; SAP, systolic arterial pressure; %SpO₂, percent oxygen saturation; XM, combination of xylazine and morphine

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Introduction

Premedication, commonly performed in animals, is an essential step before general anesthesia to calm the animal and provide anxiolysis, sedation, and preemptive analgesia, leading to a smoother anesthetic experience. In addition, premedication can reduce the anesthetic requirements needed during induction and maintenance. As a result, anesthetic side effects can be minimized and the overall quality of anesthesia improved.^{1,2} In small ruminants, such as sheep, premedication may be used for sedation to ensure safe and effective handling. To premedicate animals, neuroleptanalgesia, a combination of a sedative with an opioid, is commonly used.^{3,4} These combinations typically

include an α -2 agonist or benzodiazepine with an opioid, such as xylazine or midazolam with morphine or hydromorphone.^{3,4}

α -2 Agonists, such as xylazine, have been widely used for chemical restraint in sheep.^{1,2} As part of premedication, xylazine provides sedation, muscle relaxation, and analgesia.^{5,6} Sheep are particularly sensitive to xylazine.^{6–8} Recommended xylazine dosages for sheep are significantly lower than those for other species, ranging from 0.1 to 0.2 mg/kg.^{6,8,9} Common cardiovascular side effects include hypertension, hypotension, respiratory depression, bradycardia, arrhythmia, and reduced cardiac output.^{4,10,11} Other adverse reactions include vomiting, hypothermia, hyperglycemia, increased urine output, decreased intraocular pressure, and alterations in uterine function and endocrine activity.¹⁰ α -2 Agonists, particularly xylazine, have also been reported to cause hypoxemia.^{12–14} In Suffolk crossbred sheep breathing room air, xylazine dosages of 0.15 to 0.20 mg/kg have been associated with pulmonary edema, despite no changes in mean arterial pressure or white cell count.^{15,16} Despite these side effects, xylazine continues to be used in sheep.

Dexmedetomidine, another α -2 agonist, is frequently used in small animals and has become more commonly utilized in swine.^{17,18} Because of its higher specificity for α -2 receptors (α -1/ α -2 ratio of 1:1620) compared with xylazine (α -1/ α -2 ratio of 1:140), dexmedetomidine may produce fewer side effects than

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Table 1. Sedation score assessment

Score	Criteria
0	Standing, alert, normal behavior
1	Standing, head dropped, ataxia
2	Sternal recumbency, unable to support head, occasional attempts to attain sternal recumbency
3	Lateral recumbency, uncoordinated head and leg movements

Modified from Kästner and colleagues and Murdoch and colleagues.^{26,27}

xylazine.^{10,19,20} Dexmedetomidine has demonstrated minimal alveolar concentration-sparing effects when used with inhalant anesthetics.^{21,22} In dogs, dexmedetomidine has been used as a premedication in balanced anesthesia techniques, providing satisfactory sedation and analgesia.²³ A combination of dexmedetomidine (0.01 mg/kg) and morphine (0.3 mg/kg) as neuroleptanalgesia has been shown to provide effective analgesia for canine ovariohysterectomies.²⁴ Similarly, dexmedetomidine (0.01 mg/kg) combined with an opioid—morphine (0.5 mg/kg), meperidine (5 mg/kg), butorphanol (0.15 mg/kg), methadone (0.5 mg/kg), tramadol (5 mg/kg), or nalbuphine (0.5 mg/kg)—has been evaluated in dogs. Optimal sedation scores were observed with meperidine or methadone, while the best analgesia scores were reported with morphine, butorphanol, methadone, or nalbuphine. All agents produced similar cardiorespiratory effects.²⁵ Despite its widespread use in dogs, dexmedetomidine is rarely used in sheep.

The purpose of this study was to compare the sedative and anesthetic effects of dexmedetomidine and xylazine, each in combination with morphine, when used as premedication before anesthesia, as well as their effects on pulmonary tissues in sheep. We hypothesized that dexmedetomidine and morphine (DM) would provide profound sedation, better maintain physiologic parameters under anesthesia, and induce less lung pathology than xylazine and morphine (XM) in sheep undergoing laparoscopic surgery.

Materials and Methods

Study design. This study was conducted using a randomized experimental design to compare the sedative effects and physiologic responses of 2 different premedication drug combinations, DM and XM, in sheep undergoing isoflurane anesthesia.

Sample size. Nineteen intact male crossbred sheep (Dorper × Santa Inês) with a mean age of 219.4 ± 15.8 d and body weight of 27.5 ± 1.0 kg were included. The sample size was determined based on previous studies assessing sedation and anesthesia in small ruminants.^{11,12}

Inclusion and exclusion criteria. Food and water were withheld for 24 and 12 h, respectively, before anesthetic induction. A general physical examination and laboratory screening tests, including a complete blood count and blood chemistry profile, confirmed that all sheep were in good health.

Randomization. Nineteen sheep were randomly assigned to 1 of 2 treatment groups (DM group, $n = 10$; XM group, $n = 9$) using a computer-generated randomization table.

Blinding. Sedation scores were assessed by 3 blinded veterinarians.

Outcome measures. Sedation scores were assessed using a sedation scoring system (modified from Kästner and colleagues and Murdoch and colleagues) ranged from 0 (no sedation) to 3 (heavy sedation) (Table 1).^{26,27} The tiletamine/zolazepam dosage (mg/kg, intravenous) required to achieve successful endotracheal intubation in sheep was recorded, based on the loss of jaw tone and airway reflex. Physiologic parameters were recorded every 10 min over a 60-min period (T0 to T60). These included percent oxygen saturation (%SpO₂), heart rate (HR), respiratory rate (RR), indirect blood pressure (left forelimb; systolic arterial pressure [SAP], mean arterial pressure [MAP], and diastolic arterial pressure [DAP]), end-tidal carbon dioxide (EtCO₂), and body temperature. The isoflurane concentration (in 100% O₂) required to prevent movement during the 60-min anesthetic period was recorded every 10 min throughout the procedure. For blood gas analysis, arterial blood samples were collected from the auricular artery at preintubation (prior to anesthetic induction), T5 min, and T60 min using heparin-coated syringes (Heparin Injection BP, Gland Pharma, Hyderabad, India). Lung pathology was assessed by a pathologist through both gross and histopathologic examination. For gross pathology, pulmonary alterations were evaluated separately for each lung lobe (right cranial, right middle, right caudal, left cranial, and left caudal lobes). Gross pulmonary changes included pulmonary edema, congestion, and hemorrhage. The severity of lesions was graded using a 5-tier scale: 0, no gross changes; 0.5, minimal; 1, moderate; 1.5, marked; and 2, severe macroscopic changes (Table 2). A macroscopic lobar change score was calculated as the sum of individual scores for each lobe. The total possible score for the right lung lobes ranged from 0 to 6, whereas that for the left lung lobes ranged from 0 to 4 (modified from Adam and colleagues).²⁸ For histopathology, lung tissues were collected in a 10% buffered formalin fixative solution following the gross examination. Representative right lung tissue samples were obtained from the cranial, middle, and caudal lobes, while left lung samples were taken from the cranial and caudal lobes. After fixation, tissues were routinely processed, embedded in paraffin, sectioned (4 µm), and stained with hematoxylin and eosin. Standard histopathologic changes were

Table 2. Macroscopic lung lesion score

Score	Severity	Gross findings
0	No	The lung lobes are evenly pink and spongy; the cut surfaces show no fluid, congestion, or hemorrhage
0.5	Minimal	Foam or frothy exudate extends to the trachea or fills the main bronchi, and/or discoloration is present in a lobe, with slight fluid oozing from the cut surface, minimal congestion, or minimal hemorrhage
1	Mild	The cut surface of the lobe is moist, with slight fluid oozing from the cut surface; foam or frothy exudate is generally present, oozing from the cut surface; foam or frothy exudate is also observed in the trachea, with mild congestion or focal/small areas of hemorrhage
1.5	Mild to moderate	The lobe is congested and partially condensed (increased density and firmness); a variable amount of fluid oozes from the cut surface; foam or frothy exudate is present in the trachea, with mild to moderate congestion and multifocal petechial hemorrhages
2	Moderate	The lobe is congested, heavy, and exhibits a mildly condensed consistency; fluid oozes from the cut surface, with moderate congestion and multifocal ecchymotic hemorrhages

Modified from Adam and colleagues.²⁸

Table 3. Histopathologic lung score

Score	Severity	Histologic findings
1	Minimal	Less than half of the alveoli exhibit pulmonary edema or hemorrhage, and fewer than one-fifth of the alveoli show marked changes
2	Mild	No more than two-thirds of the alveoli exhibit pulmonary edema or hemorrhage, and fewer than one-fifth of the alveoli show marked changes
3	Moderate	At least one-fifth of the alveoli exhibit pulmonary edema or hemorrhage, and fewer than one-fifth of the alveoli show marked changes
4	Marked	Small areas show no or only modest edema or hemorrhage; more than half of the alveoli show marked changes
5	Severe	The entire lung section is diffusely affected

Modified from Adam and colleagues.²⁸

examined under a light microscope (Eclipse Ci; Nikon, Tokyo, Japan), and the severity of pathologic changes was evaluated using a histologic scoring system (Table 3). The severity of histopathologic changes was graded on a 5-tier scale: 1, minimal; 2, mild; 3, moderate; 4, marked; 5, severe.²⁸

Statistical analysis. Data are presented as mean $\pm$ SEM. Differences in body weight and age between the 2 groups were analyzed using unpaired-samples *t* tests. Sedation scores, gross lesion scores, and histologic scores were presented as median (IQR) and analyzed using the Mann-Whitney *U* test. To compare physiologic parameters between groups, the Shapiro-Wilk test was used to confirm the normal distribution of the data, followed by a 2-way repeated-measures ANOVA and a Tukey multiple comparison test. A *P* value <0.05 was considered statistically significant. All data analyses were conducted using GraphPad Prism software (GraphPad Software, La Jolla, CA).

Experimental animals. This study was reviewed and approved by the Chulalongkorn University Laboratory Animal Center Animal Care and Use Committee (IACUC approval no. 2231034). All sheep in this study were obtained from the Large Animal Department at Chulalongkorn University in Nakhon Pathom, Thailand.

Experimental procedures. The sheep were premedicated via intramuscular injection with morphine (0.3 mg/kg, 10 mg/mL; morphine sulfate injection, M&H Manufacturing, Samut Prakan, Thailand) combined with either dexmedetomidine (0.006 mg/kg, 0.5 mg/mL; Dexdomitor, Virbac, Pak Kret, Thailand) or xylazine (0.1 mg/kg, 100 mg/mL; X-Lazine, L.B.S. Laboratory, Bangkok, Thailand). Intravenous catheterization was performed via the right cephalic vein, and fluid (0.9% NaCl, 10 mL/kg/h) was administered when the sheep were in lateral recumbency or for 20 min following premedication administration. Before anesthetic induction, the first arterial blood sample for blood gas analysis (preintubation) was collected from the auricular artery. Anesthesia was induced via slow intravenous titration of tiletamine/zolazepam (50 mg/mL tiletamine and 50 mg/mL zolazepam; Zoletil, Virbac, Pak Kret, Thailand) until an adequate anesthetic depth was achieved for endotracheal intubation (6.0 to 7.0 mm diameter; Maxi Care, Zhanjiang Star Enterprise, Zhanjiang, China). Following intubation (T0), all sheep were mechanically ventilated with 100% oxygen to maintain EtCO₂ between 35 and 45 mm Hg (Comen AX-400 anesthesia workstation with inbuilt ventilator, Shenzhen Comen Medical Instruments, Shenzhen, China). Ventilator settings included an

RR of 10 to 12 breaths per minute, peak inspiratory pressure of 15 to 20 cmH₂O, positive end-expiratory pressure of 3 to 5 cmH₂O, an inspiratory-to-expiratory ratio of 1:2, and a tidal volume of 10 to 15 mL/kg. Anesthesia was maintained with isoflurane (Attane, Piramal Critical Care, Bethlehem, PA). An anesthetic monitoring device (Comen C80 multiparameter patient monitor, Shenzhen Comen Medical Instruments, Shenzhen, China) was connected to each sheep, including a pulse oximeter, esophageal temperature probe, oscillometric blood pressure cuff, and capnometer (CapnoEasy, Beijing Winland Medical, Beijing, China). A gastric tube was placed during anesthesia, and isoflurane administration was carefully monitored and recorded throughout the procedure. The second and third arterial blood samples for blood gas analysis were collected at 5 min (T5) and 60 min (T60) postintubation. Data collection concluded at T60. Following laparoscopic surgery, the sheep were euthanized with an overdose of propofol followed by potassium chloride administration, and lung tissue samples were collected from each lung lobe.

Results

Sedation scores and induction dose. The sedation scores for the DM (0.8 [0.4 to 1.0]) and XM (1.0 [1.0 to 1.0]) groups were not significantly different (Table 4). Similarly, the induction doses of tiletamine/zolazepam for the DM (1.39 $\pm$ 0.14 mg/kg) and XM (1.09 $\pm$ 0.13 mg/kg) groups also showed no significant difference (Table 4).

Physiologic parameters and isoflurane requirement. For both groups, %SpO₂ remained $>95\%$, and EtCO₂ was maintained within the range of 35 to 45 mm Hg. Comparisons between the DM and XM groups showed no significant differences in RR (12 $\pm$ 0 and 11 $\pm$ 0 breaths/min, respectively), SAP (104 $\pm$ 2 and 105 $\pm$ 1 mm Hg, respectively), MAP (75 $\pm$ 2 and 76 $\pm$ 1 mm Hg, respectively), DAP (53 $\pm$ 2 and 56 $\pm$ 1 mm Hg, respectively), or body temperature (100.5 $\pm$ 0.3 °F and 99.7 $\pm$ 0.3 °F, respectively) (Table 5). However, at T10, the HR in DM-treated sheep (84 $\pm$ 3 beats/min) was significantly higher than that in XM-treated sheep (71 $\pm$ 4 beats/min) (*P* = 0.017). The mean HR in DM-treated sheep (79 $\pm$ 1 beats/min) was also significantly higher than that in XM-treated sheep (70 $\pm$ 1 beats/min) (*P* < 0.001). At T0, the isoflurane requirement was significantly lower in DM-treated sheep (0.2% $\pm$ 0.1%) than in XM-treated sheep (0.7% $\pm$ 0.2%) (*P* = 0.029). However, this difference in the isoflurane requirement was not observed after T0 until T60, nor in the average usage throughout anesthesia (Table 5).

Blood gas analysis. Blood gas analysis was performed at 3 time points, that is, preintubation, T5, and T60, to compare the DM and XM groups at each stage. All observed blood gas parameters, including pH, partial pressure of carbon dioxide,

Table 4. Number, age, sex, sedation score, and tiletamine/zolazepam induction dose for sheep premedicated with DM or XM

Variables	DM	XM	<i>P</i> value
Number of sheep	10	9	
Age, d (mean $\pm$ SEM)	232.5 $\pm$ 26.7	204.8 $\pm$ 15.5	0.396
Body weight, kg (mean $\pm$ SEM)	26.38 $\pm$ 1.66	28.78 $\pm$ 1.18	0.265
Sedation score (median (IQR))	0.8 (0.4–1.0)	1.0 (1.0–1.0)	0.254
Total induction dose, mg/kg (mean $\pm$ SEM)	1.39 $\pm$ 0.14	1.09 $\pm$ 0.13	0.139

DM, combination of dexmedetomidine and morphine; XM, combination of xylazine and morphine.

Table 5. Physiologic parameters (mean $\pm$ SEM) for sheep premedicated with DM or XM

Parameters	Drug	Time after endotracheal intubation							Mean
		T0	T10	T20	T30	T40	T50	T60	
Temperature ($^{\circ}$ F)	DM	101.8 $\pm$ 0.5	101.6 $\pm$ 0.7	101.1 $\pm$ 0.5	100.5 $\pm$ 0.6	99.8 $\pm$ 0.5	99.3 $\pm$ 0.6	99.0 $\pm$ 0.6	100.5 $\pm$ 0.3
	XM	101.1 $\pm$ 0.4	100.7 $\pm$ 0.4	100.2 $\pm$ 0.5	99.8 $\pm$ 0.6	99.3 $\pm$ 0.6	98.6 $\pm$ 0.8	98.3 $\pm$ 0.7	99.7 $\pm$ 0.3
HR (beats/min)	DM	80 $\pm$ 8	84 $\pm$ 3*	82 $\pm$ 3	80 $\pm$ 3	78 $\pm$ 3	78 $\pm$ 3	78 $\pm$ 3	79 $\pm$ 1*
	XM	75 $\pm$ 5	71 $\pm$ 4*	70 $\pm$ 5	69 $\pm$ 5	68 $\pm$ 4	69 $\pm$ 4	70 $\pm$ 4	70 $\pm$ 1*
RR (breaths/min)	DM	11 $\pm$ 2	12 $\pm$ 3	12 $\pm$ 2	13 $\pm$ 3	11 $\pm$ 2	11 $\pm$ 2	11 $\pm$ 2	12 $\pm$ 0
	XM	10 $\pm$ 2	11 $\pm$ 2	10 $\pm$ 1	11 $\pm$ 2	11 $\pm$ 3	12 $\pm$ 4	12 $\pm$ 3	11 $\pm$ 0
SAP (mm Hg)	DM	120 $\pm$ 8	106 $\pm$ 7	104 $\pm$ 6	107 $\pm$ 7	98 $\pm$ 7	97 $\pm$ 6	98 $\pm$ 7	104 $\pm$ 2
	XM	113 $\pm$ 9	99 $\pm$ 8	100 $\pm$ 4	108 $\pm$ 6	106 $\pm$ 8	101 $\pm$ 8	104 $\pm$ 9	105 $\pm$ 1
MAP (mm Hg)	DM	91 $\pm$ 8	76 $\pm$ 6	71 $\pm$ 6	74 $\pm$ 7	72 $\pm$ 7	71 $\pm$ 6	74 $\pm$ 7	75 $\pm$ 2
	XM	83 $\pm$ 10	69 $\pm$ 7	75 $\pm$ 5	76 $\pm$ 5	76 $\pm$ 7	71 $\pm$ 7	80 $\pm$ 9	76 $\pm$ 1
DAP (mm Hg)	DM	74 $\pm$ 8	57 $\pm$ 6	50 $\pm$ 6	52 $\pm$ 6	49 $\pm$ 4	50 $\pm$ 5	52 $\pm$ 5	53 $\pm$ 2
	XM	58 $\pm$ 12	53 $\pm$ 8	53 $\pm$ 6	59 $\pm$ 6	54 $\pm$ 6	52 $\pm$ 5	63 $\pm$ 9	56 $\pm$ 1
Isoflurane (%)	DM	0.2 $\pm$ 0.1*	0.5 $\pm$ 0.2	0.6 $\pm$ 0.2	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.5 $\pm$ 0.0
	XM	0.7 $\pm$ 0.2*	0.3 $\pm$ 0.1	0.5 $\pm$ 0.1	0.4 $\pm$ 0.1	0.4 $\pm$ 0.1	0.4 $\pm$ 0.1	0.4 $\pm$ 0.1	0.5 $\pm$ 0.0

DAP, diastolic arterial pressure; DM, combination of dexmedetomidine and morphine; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SAP, systolic arterial pressure; XM, combination of xylazine and morphine.

* $P < 0.05$ between groups.

partial pressure of oxygen, Na^+ , K^+ , Cl^- , actual bicarbonate concentration, standard bicarbonate concentration, base excess of extracellular fluid, base excess, total plasma carbon dioxide content, anion gap, and $\%\text{SpO}_2$, showed no significant differences over time (Table 6).

Lung pathology. Gross evaluation. Macroscopically, lung tissues exhibited a range of lesions, from no changes or slight alterations (score 0) to moderate pulmonary hemorrhage and edema (scores 1.5 to 2.0) in both experimental groups (Figure 1). The macroscopic lung lesion scores are presented in Table 7. Although the lung lesion scores in the XM group appeared higher than those in the DM group, this difference was not statistically significant.

Histologic evaluation. Histologic findings revealed minimal to marked pulmonary changes (scores 1 to 4). Pulmonary congestion and hemorrhage were observed in both groups, along with mild to moderate pulmonary edema (Figure 1). Histologic scores were significantly higher in the XM group than in the

DM group for both the right and left lung lobes. In addition, the XM group had a significantly higher score in the left cranial lung lobe, as well as a higher total score for the left lung lobe ($P = 0.029$ and $P = 0.045$, respectively) (Table 8). However, no significant differences were observed between the DM and XM groups for other lung lobes, including the right cranial, right middle, right caudal, and left caudal lobes.

Discussion

Both DM and XM exhibited comparable sedation in sheep undergoing general anesthesia; required a similar amount of induction drug (tiletamine/zolazepam); did not alter physiologic parameters (except HR) or arterial blood gas parameters throughout the study (60 min), with the average HR in the DM group higher than that in the XM group; required a similar isoflurane level ($\sim 0.5\%$) except at T0, at which timepoint the DM group required a lower isoflurane level; and showed no differences in gross pathology, while

Table 6. Blood gas parameters (mean $\pm$ SEM) in sheep premedicated with DM or XM

Parameter	Preintubation			T5			T60		
	DM	XM	<i>P</i> value	DM	XM	<i>P</i> value	DM	XM	<i>P</i> value
pH	7.49 $\pm$ 0.01	7.53 $\pm$ 0.01	0.111	7.51 $\pm$ 0.03	7.51 $\pm$ 0.02	0.893	7.50 $\pm$ 0.05	7.41 $\pm$ 0.02	0.125
paCO_2	33.03 $\pm$ 1.08	31.62 $\pm$ 1.91	0.518	36.34 $\pm$ 3.36	35.50 $\pm$ 2.22	0.841	41.37 $\pm$ 4.43	45.32 $\pm$ 3.76	0.510
paO_2	69.07 $\pm$ 5.49	83.38 $\pm$ 12.82	0.302	298.62 $\pm$ 28.11	350.36 $\pm$ 37.63	0.280	337.34 $\pm$ 23.48	350.40 $\pm$ 14.28	0.650
Na^+	132.80 $\pm$ 1.13	133.33 $\pm$ 2.20	0.827	135.80 $\pm$ 1.23	135.22 $\pm$ 1.22	0.744	133.70 $\pm$ 1.64	131.44 $\pm$ 1.65	0.347
K^+	2.98 $\pm$ 0.13	3.02 $\pm$ 0.18	0.878	2.83 $\pm$ 0.14	3.04 $\pm$ 0.17	0.362	2.64 $\pm$ 0.17	2.62 $\pm$ 0.16	0.928
Cl^-	94.80 $\pm$ 1.69	91.22 $\pm$ 2.38	0.229	98.40 $\pm$ 2.03	95.44 $\pm$ 2.01	0.317	96.40 $\pm$ 2.15	90.56 $\pm$ 2.33	0.083
HCO_3act	24.85 $\pm$ 0.96	25.59 $\pm$ 1.27	0.644	27.22 $\pm$ 0.96	27.48 $\pm$ 0.70	0.834	29.28 $\pm$ 1.33	27.66 $\pm$ 1.54	0.433
HCO_3std	25.89 $\pm$ 0.91	27.07 $\pm$ 0.99	0.395	27.96 $\pm$ 0.65	28.29 $\pm$ 0.58	0.712	29.44 $\pm$ 1.00	27.08 $\pm$ 1.14	0.136
BE-esf	1.60 $\pm$ 1.11	2.90 $\pm$ 1.25	0.447	4.15 $\pm$ 0.79	4.51 $\pm$ 0.70	0.740	6.03 $\pm$ 1.16	3.04 $\pm$ 1.40	0.117
BE-B	1.59 $\pm$ 1.01	2.88 $\pm$ 1.10	0.400	3.84 $\pm$ 0.70	4.19 $\pm$ 0.63	0.719	5.39 $\pm$ 1.08	2.76 $\pm$ 1.27	0.130
ctCO_2	25.88 $\pm$ 0.98	26.57 $\pm$ 1.33	0.680	28.34 $\pm$ 1.05	28.58 $\pm$ 0.75	0.859	30.55 $\pm$ 1.43	29.07 $\pm$ 1.64	0.503
AnGap	16.23 $\pm$ 1.73	19.39 $\pm$ 1.99	0.246	12.77 $\pm$ 2.10	15.54 $\pm$ 1.89	0.343	10.91 $\pm$ 2.03	15.91 $\pm$ 2.40	0.128
$\%\text{SpO}_2$	92.56 $\pm$ 2.60	95.03 $\pm$ 1.32	0.423	99.67 $\pm$ 0.06	99.63 $\pm$ 0.19	0.851	99.76 $\pm$ 0.03	99.70 $\pm$ 0.04	0.250

AnGap, anion gap; BE-B, base excess; BE-esf, base excess of extracellular fluid; ctCO_2 , total plasma content of carbon dioxide; DM, combination of dexmedetomidine and morphine; HCO_3act , actual bicarbonate concentration; HCO_3std , standard bicarbonate concentration; paCO_2 , partial pressure of carbon dioxide; paO_2 , partial pressure of oxygen; $\%\text{SpO}_2$, oxygen saturation. XM, combination of xylazine and morphine.

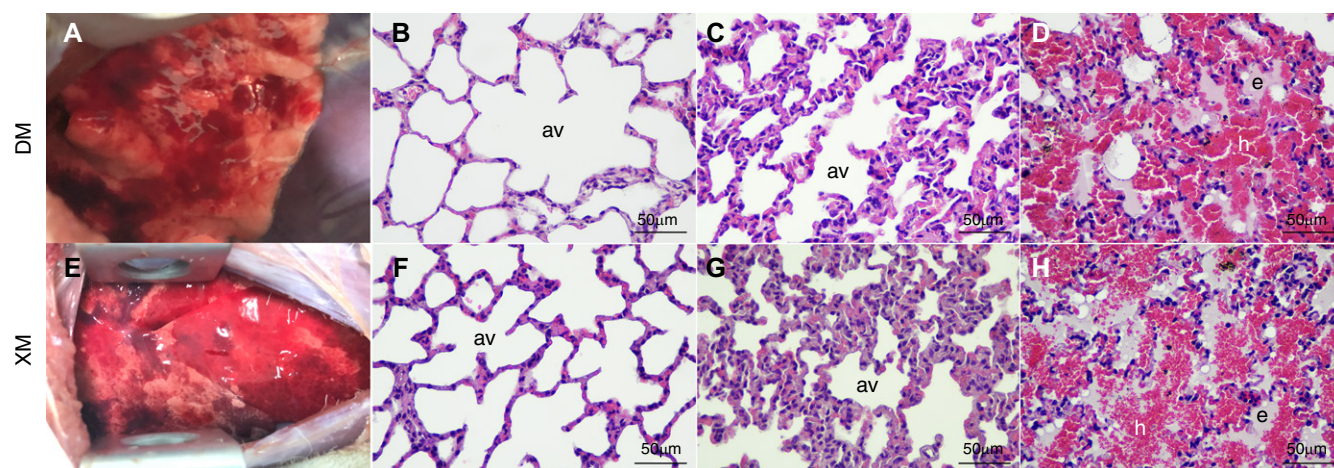


Figure 1. Macroscopic findings of sheep in the dexmedetomidine/morphine (DM) (A) and xylazine/morphine (XM) (E) groups demonstrated areas of congestion and hemorrhage. Similarly, histologic images from the DM and XM groups depict normal lung structure (B and F), congestion (C and G), and multifocal areas of edema and hemorrhage (D and H). Scale bar = 50 μ m. av, normal alveolar space; e, edematous fluid; h, hemorrhage.

histologic evaluation revealed mild to moderate pulmonary edema in XM-treated sheep.

To our knowledge, this is the first study to use DM and XM as sedative combinations in sheep. Because α -2 agonists have been reported to cause adverse pulmonary effects, the lowest possible dosages were selected to achieve sedation. The dexmedetomidine dosage (0.006 mg/kg, IM) was determined based on a pilot study and was significantly lower than the recommended dosage range for sheep (0.01 to 0.03 mg/kg).⁶ The pilot study demonstrated that this dosage was sufficient for handling sheep, placing intravenous catheters, collecting arterial blood samples, and administering preoxygenation via a mask. The xylazine dosage (0.1 mg/kg) was selected from the lower range of recommended dosages for sheep (0.1 to 0.3 mg/kg).⁶

Neuroleptanalgesia combines sedatives with opioids, allowing for lower doses of each drug and reducing side effects. Therefore, an opioid, morphine (0.3 mg/kg), was included.²⁹ Although the combination of morphine and α -2 agonists was expected to produce profound sedation, both DM and XM only provided mild sedation 20 min after administration. Dexmedetomidine's sedative effects have been reported to be similar to those of medetomidine (0.006 mg/kg), producing light to moderate sedation lasting up to 60 min, while xylazine-induced sedation typically lasts 10 to 20 min.³⁰ Despite causing only mild sedation in sheep, both DM and XM sufficiently reduced the subsequent anesthetic induction dose of tiletamine/zolazepam (~1.0 to 1.4 mg/kg). The tiletamine/zolazepam

dosages required in this study were considerably lower than the recommended sheep dosage for anesthesia (12 to 24 mg/kg, IM).^{31,32} Notably, the tiletamine/zolazepam dosage used in this study was intended to facilitate rapid and smooth anesthetic induction, allowing for endotracheal intubation. In addition, both DM and XM reduced the isoflurane requirement to 0.5% throughout the 60-min monitoring period. This low isoflurane level is ~0.3-fold the minimal alveolar concentration for sheep, which ranges from 1.42% to 1.58%.³³ Similarly, dexmedetomidine (0.005 mg/kg, IV) has been shown to reduce the isoflurane requirement to ~1% in female sheep.³⁴

The physiologic parameters (RR, SAP, MAP, DAP, and body temperature) and blood gas analysis showed no significant differences between the DM and XM groups. However, dexmedetomidine (0.002 mg/kg, IV) has been reported to initially increase MAP and systemic vascular resistance, followed by a decrease over a 90-min period in sheep.³⁵ The one physiologic parameter that differed was HR (at T10 and average HR), with DM-treated sheep exhibiting a higher mean HR than XM-treated sheep. Interestingly, in female sheep administered dexmedetomidine (0.005 mg/kg, IV), HR was not significantly affected.³⁴ This effect may be attributed to dexmedetomidine's higher α -2 receptor selectivity, lower dose, and intramuscular (compared with intravenous) administration. Importantly, note that in other species, α -2 agonists (for example, dexmedetomidine, xylazine) can cause adverse effects such as hypertension followed by

Table 7. Macroscopic lung lesion score (median (IQR)) for sheep premedicated with DM or XM

Lung lobe	DM	XM	P value
Right lobe			
Cranial part	0.00 (0.00–0.31)	0.50 (0.00–1.50)	0.256
Middle part	0.00 (0.00–0.31)	0.50 (0.00–1.50)	0.256
Caudal part	0.00 (0.00–0.31)	0.50 (0.00–1.50)	0.256
Total score	0.00 (0.00–0.94)	1.50 (0.00–4.50)	0.256
Left lobe			
Cranial part	0.00 (0.00–0.75)	1.50 (0.25–1.75)	0.160
Caudal part	0.00 (0.00–0.75)	1.50 (0.25–1.75)	0.160
Total score	0.00 (0.00–1.55)	3.00 (0.50–3.50)	0.283

DM, combination of dexmedetomidine and morphine; XM, combination of xylazine and morphine.

Table 8. Histopathological lung score (median (IQR)) in sheep premedicated with DM or XM

Lung lobe	DM	XM	P value
Right lobe			
Cranial part	1.00 (1.00–2.00)	2.00 (2.00–3.00)	0.103
Middle part	1.00 (1.00–2.00)	2.00 (1.00–2.00)	0.306
Caudal part	2.00 (1.00–2.00)	2.00 (2.00–3.00)	0.080
Total score	5.00 (3.00–5.00)	6.00 (6.00–7.00)	0.009*
Left lobe			
Cranial part	1.00 (1.00–2.00)	2.00 (2.00–3.00)	0.029*
Caudal part	2.00 (1.00–2.00)	3.00 (2.00–3.00)	0.072
Total score	3.00 (2.00–5.00)	5.00 (4.00–5.00)	0.045*

DM, combination of dexmedetomidine and morphine; XM, combination of xylazine and morphine.

* $P < 0.05$ between groups.

hypotension, hypothermia, and respiratory depression.^{4,10,11} In this study, blood pressure remained within a normal range (~75 mm Hg) throughout the 60-min anesthetic period, with no signs of hypertension or hypotension. In addition, body temperature (99 to 100 °F) and EtCO₂ (35 to 45 mm Hg) were maintained.

Interestingly, our study revealed pulmonary lesion differences between the 2 groups. Although gross lesion scores were higher in the XM group, these differences were not statistically significant. In contrast, XM-treated sheep exhibited significantly worse histopathologic scores, with pulmonary congestion, hemorrhage, and edema. DM-treated sheep had lower histopathologic scores, indicating fewer lesions. Similarly, in another study, xylazine (0.5 mg/kg, IV) did not cause gross lesions (macroscopic edema) in sheep.²⁸ However, xylazine has been reported to induce pulmonary edema and/or alterations in partial pressure of arterial O₂ (PaO₂) in sheep (0.15 mg/kg, IV),^{9,16} calves (0.3 mg/kg, IV),³⁶ and rats.^{37–39} Medetomidine (0.03 mg/kg, IV) has also been reported to lower PaO₂ in calves.³⁶ Dexmedetomidine (0.002 mg/kg, IV) has been shown to increase mean pulmonary arterial pressure, pulmonary arterial occlusion pressure, and capillary pressure within 2 min, with CT imaging revealing increased lung density.⁴⁰ The same study also reported vascular congestion followed by protein and erythrocyte extravasation into alveoli.⁴⁰ In addition, dexmedetomidine has been associated with ventilator-induced lung injury in male Sprague–Dawley rats.⁴¹ Potential mechanisms underlying these effects include bronchospasm triggered by direct stimulation of peripheral α -2 adrenergic receptors, pulmonary microembolism due to platelet aggregation associated with α -2 adrenergic receptors, and activation of pulmonary intravascular macrophages.¹⁶ These processes collectively contribute to acute lung injury and subsequent alterations in respiratory mechanics.^{13,36} Our study showed no differences between left and right lung lesions; both lungs exhibited similar lesions and scores, regardless of group. All sheep were positioned in dorsal recumbency throughout the procedure, eliminating potential orthostatic effects on the lungs. These results are consistent with another study that also reported evenly distributed lung lesions.²⁸ Although XM-associated severity was histopathologically evident in our study, neither the PaO₂ (~300 mm Hg under 100% O₂) nor %SpO₂ in either the DM or XM group indicated hypoxemia or showed significant differences. Similarly, in another study, dexmedetomidine (0.005 mg/kg, IV) resulted in PaO₂ values of ~220 to 279 mm Hg on 100% O₂ in female sheep.^{28,34} That study also concluded that histologic severity did not correlate with %SpO₂, which aligns with our findings.²⁸ Dexmedetomidine (0.002 mg/kg, IV) has been reported to significantly reduce PaO₂ for up to 10 min in anesthetized sheep.^{35,42} However, the unaltered PaO₂ results in our study were consistent with another study using xylazine (0.4 mg/kg, IV) or medetomidine (0.004 mg/kg, IV) in horses.⁴³ α -2 Antagonists, including atipamezole (0.04 to 0.10 mg/kg, IV), yohimbine (0.125 mg/kg, IV), and vatinoxan (0.75 mg/kg, IV), have been shown to partially reverse these adverse effects in sheep.²⁸ Because the sheep in our study were euthanized, α -2 antagonists were not administered. Our findings suggest that dexmedetomidine may offer a more favorable pulmonary profile, potentially reducing anesthesia-associated respiratory complications. Its selective action on α -2 adrenergic receptors, sparing α -1 receptors, may mitigate the adverse pulmonary effects observed with xylazine, making dexmedetomidine a preferable choice for premedication in sheep.

Despite these promising findings, our study had several limitations. First, physiologic parameters were not measured beyond 60 min because the primary goal was to assess the use

of DM and XM for premedication. Consequently, we focused on monitoring sedation effects in relation to the induction dose, isoflurane requirements, and physiologic and blood gas parameters for only 60 min following DM or XM administration. Anesthetic recovery quality was not assessed because this was a collaborative terminal study, and the sheep did not recover. Only male sheep were used, and anesthetic effects may vary by sex.^{44,45} Furthermore, only single and low dosages of DM and XM were studied. Higher dosages or different combinations may have altered the results, particularly regarding lung pathology. In addition, the reversal agent atipamezole was not used. While atipamezole reportedly reverses these adverse effects, its ability to reverse α -2-induced pulmonary edema remains unknown. Lastly, although ventilatory settings were standardized across all animals, the potential influence of the laparoscopic procedure or mechanical ventilation on the observed pulmonary changes cannot be ruled out.

In conclusion, our study demonstrates that both DM and XM combinations are effective premedication protocols in sheep, providing comparable levels of sedation and maintaining stable physiologic and blood gas parameters throughout anesthesia. The DM combination was associated with fewer pulmonary complications, suggesting a potentially safer respiratory profile. In addition, the DM group exhibited a higher mean HR, which may be advantageous in minimizing bradycardia. These findings support the use of dexmedetomidine as a viable alternative to xylazine for premedication of sheep, particularly in cases where cardiopulmonary side effects are a concern.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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